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09/424,705	06/02/2000	MELVYN LITTLE	35280047US00	8422

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EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 09/05/2003

36

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/424,705

Applicant(s)

LITTLE ET AL.

Examiner

Jessica H. Roark

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 June 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,4-7,9,12-14,19-21,23-26,28 and 29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-7,9,12-14,19-21,23-26,28 and 29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 September 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

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### RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/20/03 (Paper No. 35), has been entered.  
Claims 2-3, 8, 10-11, 15-18, 22 and 27 have been cancelled in this or a previous amendment.  
Claims 1 and 4 have been amended.  
Claims 28-29 have been added.  
Claims 1, 4-7, 9, 12-14, 19-21, 23-26 and 28-29 are pending and under consideration in the instant application.

2. This Office Action will be in response to applicant's arguments, filed 6/20/03 (Paper No. 35).  
The rejections of record can be found in a previous Office Action (Paper Nos. 13, 19, 27 and 33).  
It is noted that New Grounds of Rejection are set forth herein.

### *Objections to the Specification*

3. The specification is objected to under 37 CFR 1.821(d) because SEQ ID NOS are not disclosed in the Brief Description of the Drawings for all sequences. Appropriate correction is required.

Applicant's amendment to the Brief Description of the Drawings, filed 6/20/03, is acknowledged. However, Figures 2, 3A and 3B each present both nucleic acid and amino acid sequences. Therefore, the Brief Description must provide sequence identifiers for both the nucleic acid and amino acid sequences.

### *Claim Rejections - 35 USC § 112 second paragraph*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.  
*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

5. Claim 4-7, 9, 12-14 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step that results in the serine found at position H100A of the product set forth in claim 1, as required by the recitation of SEQ ID NO:2 in claim 1.

Applicant's comments, filed 6/20/03, regarding the amendment to claim 4 are acknowledged. However, it is noted that amended step 4d still only results in substitution with "a polar amino acid". Because claim 1, from which claim 4 depends requires the amino acid sequence of SEQ ID NO:2, claim 4 still omits the step required to produce the sequence recited in claim 1.

It is suggested that Applicant amend step 4(d) to require that the cysteine is substituted with the polar amino acid serine.

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B) Claim step 4(e) and dependent claims 5-7, 9, 12-14 and 19-21 recite "the mutated cDNA obtained n c)". However, there is a lack of antecedent basis because no mutated cDNA is recited n step 4c) as amended. It is suggested that Applicant amend step 4(e) to depend from step 4(d).

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

***35 USC § 112 first paragraph***

6. Applicant's amendment, filed 6/20/03 has obviated the previous rejection of claims 1-2, 4-7, 9, 12-14, and 19-21 under 35 U.S.C. 112, first paragraph *New Matter*.

***Claim Rejections – 35 U.S.C. § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 4-6, 9, 12, 19-20, 23-25 and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992, of record) in view of Senoo et al (US Pat. No. 5,852,177, of record) and Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4).

Applicant's argument, filed 6/20/03, have been fully considered but have not been found convincing.

Applicant's arguments are addressed below in the context of the rejection of record as modified to address the newly added claim limitations.

The instant claims are drawn to an antibody comprising the amino acid sequence depicted by SEQ ID NO:2, which depicts a scFv form of the heavy and light chains of the OKT3 antibody (CRL 8001) in which the cysteine at position H100A has been exchanged with the polar amino acid serine. The claims are also drawn to a method of producing this antibody.

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Kroon et al. review the art-recognized therapeutic applications of the OKT3 antibody and the art-recognized problems associated with long term storage of the OKT3 antibody (e.g., "Introduction" on page 1386). Kroon et al. teach that the OKT3 antibody is inactivated while in storage as a consequence of formation of cross-links between heavy chain in the region of amino acids 99-121 (see entire document, especially page 1391-1392 bridging paragraph and the sequence of Figure 1). Although the numbering system used is different, Kroon et al. teach that the Cys in the third heavy chain CDR (i.e., CDR3) *is a likely candidate* for oxidation which would lead to degradative structural changes for OKT3 (see especially page 1390). Kroon et al. clearly indicate on page 1390 that "[t]he most significant change in the peptide maps of OKT3 with long term storage was a decrease in the size of the peak corresponding to H99-121" and that "there is a non-disulfide-bonded Cys at residue 105, a likely candidate for oxidation."

Kroon et al. further teach that using site directed mutagenesis to synthesize more stable analogues would be beneficial for the development of therapeutics (e.g., page 1392, last paragraph).

Thus Kroon et al. provide guidance to replace the heavy chain CDR3 cysteine which decreases OKT3 stability and is the same cysteine as that at position H100A using the instant numbering system. Kroon et al. further teach the application of site-directed mutagenesis as a method of replacing the cysteine and generating more stable forms of OKT3.

Consequently, one of ordinary skill in the art at the time the invention was made, armed with the teachings of Kroon et al., would have been motivated to change the cysteine at position H100A (Kabat numbering system) in CDR3 of the OKT3 heavy chain by site-directed mutagenesis.

Kroon et al. do not teach that the cysteine at position H100A of the OKT3 antibody should be replaced with the polar amino acid serine.

However, Senoo et al. teach that formation of intra and interchain disulfide bonds is detrimental to protein stability (see entire document, especially column 1 to column 2, bridging paragraph) and that the conversion of a cysteine to serine eliminates this problem and improves protein stability (e.g., column 7, lines 55-57).

Thus the ordinary artisan at the time the invention was made would have been motivated to select serine in particular as the amino acid to replace the cysteine at H100A in mutagenesis of the OKT3 antibody.

Kroon et al. also do not teach a detailed method of producing a recombinant antibody product in which the cysteine at position H100A of the OKT3 antibody has been exchanged with the polar amino acid serine, nor do they produce OKT3 having the cysteine at H100A changed to a serine. Neither do Kroon et al. teach the amino acid sequence depicted in SEQ ID NO:2.

Kipriyanov et al. teach a method of producing scFv from hybridomas of interest by obtaining mRNA, transcribing the mRNA to cDNA, amplifying the heavy and light chain variable regions using the primers Bi5, Bi8, Bi4, and Bi3f (i.e., SEQ ID NOS: 8-11), cloning the amplified DNA into the pCR-Skript SK(+) vector adapted for site-specific mutagenesis, insertion of the DNA into the expression vector pHOG21, and finally expression of the scFv using E. Coli XL1-Blue (see entire document, especially sections 2.2 to 2.5).

The pHOG21 vector taught by Kipriyanov et al. results in the insertion of a pelB leader sequence at the amino terminus of the cloned heavy chain variable region, the insertion of a linker sequence comprising the YOL epitope between the heavy and light chain variable region sequences and the insertion of a tandemly linked c-myc and 6-His tag at the carboxy terminus of the cloned light chain variable region (see in particular figure 2 on page 57).

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Kipriyanov et al. review the art-recognized advantages of the scFv form of an antibody at the bridging paragraph of pages 51-52. Kipriyanov et al. further teach that their particular cloning approach is advantageous because the 6-His tag could be used in a rapid single-step purification of the scFv antibody (e.g., Section 3.2 on page 57, and comments on page 52, final full paragraph), and an antibody to the C-terminal c-myc tag could be used to enrich for clones containing the correct insert (e.g., Section 3.4 on page 59, and comments on page 52, final full paragraph).

Thus Kipriyanov et al. teach the desirability of the scFv form of therapeutic antibodies and an advantageous method of producing such antibodies.

It is noted that scFv antibodies are monoclonal unless intentionally modified to provide a bispecific format.

Kipriyanov et al. also demonstrate that this scFv cloning method could be successfully applied to the OKT3 antibody, because Kipriyanov et al. teach on page 57 in the right column that the an anti-CD3 scFv-dmOKT3 antibody was produced by them and that this scFv antibody still bound its CD3 antigen.

Therefore it would have been obvious to one of ordinary skill in the art to modify the method of Kipriyanov et al. to include the introduction of a mutation in which heavy chain cysteine H100A (in the instant numbering system) of the OKT3 monoclonal antibody (CRL 8001) was replaced with serine in order to obtain a more stable OKT3 antibody. Site-directed mutagenesis to produce such a molecule was well within the skill of the ordinary artisan at the time the invention was made. Primer selection and design for the mutagenesis would have been a matter of selection based upon the sequence to be mutated and the change introduced. Kroon et al. give clear direction to H100A, which is the Cys found in the third CDR of the OKT3 heavy chain. Kipriyanov et al. teach the heavy and light chain primers, cloning vector and expression system for producing a scFv form of OKT3 and show not only that a scFv of OKT3 can be produced, but that it is functional (i.e., still binds CD3). Senoo et al. teach that mutagenesis to Ser eliminates disulfide bonding detrimental to stability. Given the teachings of these references, the ordinary artisan would have had a reasonable expectation of producing a mutated OKT3 scFv in which the Cys in CDR3 (H100A) had been exchanged for cysteine using a modification of the method of Kipriyanov that included site-directed mutagenesis.

As set forth supra, Kroon et al. provide clear motivation for producing an OKT3 antibody in which the Cys in CDR3 of the heavy chain was mutated in order to improve the stability of the therapeutic OKT3 antibody; and the teachings of Senoo et al. provide motivation for selection of Ser as the replacement amino acid. Unless otherwise modified (e.g., to produce a bispecific antibody), a mutated OKT3 antibody would still be a monoclonal antibody.

Instant SEQ ID NO:2 sets forth the amino acid sequence of a scFv form of the OKT3 antibody in which the Cys found in heavy chain CDR3 has been replaced by a Ser.

SEQ ID NO:2 is comprised, from the amino to carboxy terminus, of:

- a) a pelB leader sequence, as set forth in Figure 2A of Kipriyanov et al.;
- b) the OKT3 VH bearing the Cys to Ser replacement;
- c) a linker sequence that is the linker sequence set forth in Figure 2B of Kipriyanov et al.;
- d) the OKT3 VL;
- e) a c-myc tag sequence, as set forth in Figure 2C of Kipriyanov et al.; and
- f) a 6 His tag, as set forth in Figure 2C of Kipriyanov et al.

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Components (a), (c), (e) and (f) are derived from the pHOG21 expression vector taught by Kipriyanov et al. As taught by Kipriyanov et al., an antibody VH and VL can be inserted into the pHOG21 vector sequence by amplifying the cDNA of the antibody with the primers provided in Table 1 of Kipriyanov et al. The primers taught by Kipriyanov et al. result in restriction sites that allow insertion of the antibody VH and VL sequences such that defined portions of the VH and VL chains are inserted (i.e., the primers define the fragment of the VH and VL chains inserted into the expression vector).

The amino acid sequence of the OKT3 antibody VH and VL chains is an intrinsic property of the antibody. The non-vector sequence of SEQ ID NO:2 appears to differ from that of the OKT3/CRL8001 amino acid sequence only by virtue of the Cys to Ser replacement (for which motivation to make the change exists), and by the amino and carboxy termini. However, the amino and carboxy termini are necessarily defined by the heavy and light chain primers used to amplify the heavy and light chain variable regions and the primers taught by Kipriyanov et al. necessarily result in the OKT3 VH and VL amino acid sequence components of SEQ ID NO:2.

Thus the teachings of the combination of the references also result in the amino acid sequence of the monoclonal scFv antibody set forth in SEQ ID NO:2.

Applicant has argued in the response filed 6/20/03 that Kroon et al. teach away from the substitution of the cysteine at H100A because they note on page 1390 at the 2<sup>nd</sup> paragraph of the left column that "degradative structural changes at this residue may have a significant impact on the binding affinity of the antibody". Applicant argues that the ordinary artisan would therefore avoid substitutions at this position because of the potential impact on antibody binding affinity.

However, this argument disregards the fact that the entire focus of Kroon et al. is on determining why the OKT3 antibody is susceptible to degradation, which is assayed as a loss of binding activity (see e.g., page 1389, second sentence of section "Degradation upon Storage at 2-8°C"). As discussed in detail supra, the teaching of Kroon et al., taken for all the teach, provide clear guidance and motivation with respect to the replacement of the cysteine in CDR3 of OKT3.

Applicant also argues in the Remarks filed 6/20/03 that there was no reasonable expectation that the substitution of the cysteine with a serine would result in an antibody with almost no loss in binding affinity.

However, the instant claims do not recite any requirements regarding the binding affinity of the antibody. In addition, even were limitations regarding binding affinity recited, since there is sufficient motivation and reasonable expectation regarding the production of the same antibody product as that claimed, there would be no difference in the binding affinity.

The Examiner maintains for the reasons set forth supra that the instant teaching provide such clear guidance as to the amino acid to change (the cysteine in HCDR3) and the amino acid to substitute (serine) that the ordinary artisan at the time the invention was made would have been motivated to produce the instantly recited antibody using the recited methods. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as applied to the amended claims.

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9. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992, of record) in view of Senoo et al (US Pat. No. 5,852,177, of record) and Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4) as applied to claims 1, 4-6, 9, 12, 19-20, 23-25 and 28-29 above, and in further view of Nitta et al. (The LANCET 1990; 335:368-371, IDS #9).

The claims are drawn to a bispecific antibody comprising the amino acid sequence depicted by SEQ ID NO:2.

The amendment filed 6/20/03 does not affect the rejection of record with respect to claim 26.

Applicant's argument, filed 6/20/03, have been fully considered but have not been found convincing.

Applicant argues that the teachings of Nitta et al. do not overcome the limitations discussed supra with respect to Kroon et al. in view of Senoo et al. and Kipriyanov et al.

Applicant's arguments, filed 6/20/03 regarding the teachings of Kroon et al. in view of Senoo et al. and Kipriyanov et al. have been discussed supra in the context of the reiteration of the rejection as applied to the amended claims and have not been found convincing for the reasons set forth supra.

As previously acknowledged, Kroon et al. in view of Senoo et al. and Kipriyanov et al. do not teach a bispecific antibody comprising SEQ ID NO:2.

Nitta et al. teach a bispecific antibody comprising the anti-CD3 monoclonal antibody OKT3 and how to make it (see entire document, e.g., Abstract and "Preparation of bispecific antibody" on page 368). Nitta et al. also teach the in vitro use of the bispecific antibody comprising OKT3 in the production of LAK cells which were used in adoptive transfer experiments to successfully target glioma cells in patients and were found to be more effective than LAK cells generated without the OKT3 bispecific antibody present (see entire document, as summarized in Abstract).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to substitute the more stable form of the OKT3 antibody taught by the combination of Kroon et al. Senoo et al. and Kipriyanov et al. for the unmutated antibody used in the bispecific construct of Nitta et al. in order to obtain a more stable bispecific antibody for use in in vitro generation of anti-tumor LAK cells. The ordinary artisan at the time the invention was made would have been motivated to make the substitution in order to produce a more stable antibody form of the therapeutic OKT3 antibody, which the ordinary artisan would have recognized as more desirable for use in the methods of Nitta et al. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of successfully producing a bispecific antibody comprising SEQ ID NO:2. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained as applied to the amended claims.

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*Conclusion*

10. No claim is allowed.

11. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
September 3, 2003

*Phillip Gambel*  
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